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Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials

Giuseppe De Luca*, Eliano Navarese, and Paolo Marino

Division of Cardiology, 'Maggiore della Carità' Hospital, Eastern Piedmont University 'A. Avogadro', Novara, Italy

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Aims Several randomized trials and a previous meta-analysis have shown significant benefits from Gp IIb-IIIa inhibitors, especially abciximab. Recent randomized trials (BRAVE-3 and HORIZON trials) have shown no benefits from adjunctive Gp IIb-IIIa inhibitors on the top of clopidogrel administration. However, the relatively low mortality may have hampered the conclusion of these recent trials. Thus, the aim of the current study was to perform an update meta-analysis of randomized trials on adjunctive Gp IIb-IIIa inhibitors in primary angioplasty, and to evaluate by meta-regression analysis, whether the results may be related to risk profile.

Methods and results We obtained results from all randomized trials evaluating the benefits of adjunctive Gp IIb-IIIa inhibitors among STEMI patients undergoing primary angioplasty. The literature was scanned by formal searches of electronic databases (MEDLINE and CENTRAL) from January 1990 to September 2008. The following key words were used: randomized trial, myocardial infarction, reperfusion, primary angioplasty, Gp IIb-IIIa inhibitors, abciximab, tirofiban, and eptifibatide. Clinical endpoint was mortality at 30 days. Major bleeding complications were assessed as safety endpoint. No language restriction was applied. A total of 16 randomized trials were finally included in the meta-analysis, involving 10 085 patients (5094 or 50.5% in the Gp IIb-IIIa inhibitors group and 4991 or 49.5% in the control group. Gp IIb-IIIa inhibitors did not reduce 30 day mortality (2.8 vs. 2.9%, $P = 0.75$) or re-infarction (1.5 vs. 1.9%, $P = 0.22$), but were associated with higher risk of major bleeding complications (4.1 vs. 2.7%, $P = 0.0004$). However, we observed a significant relationship between patient's risk profile and benefits from adjunctive Gp IIb-IIIa inhibitors in terms of death ($P = 0.008$) but not re-infarction ($P = 0.25$).

Conclusion This meta-analysis shows a significant relationship between benefits in mortality from Gp IIb-IIIa inhibitors and patient's risk profile. Thus, Gp IIb-IIIa inhibitors should be strongly considered among high-risk patients.

Keywords Primary angioplasty • Gp IIb-IIIa inhibitors • Meta-analysis • STEMI

Introduction

Primary angioplasty has been shown to reduce mortality when compared with thrombolysis, due to the ability to restore TIMI 3 flow in the vast majority of patients.[1] However, suboptimal reperfusion may be observed in a relatively large proportion of patients despite TIMI 3 flow, mainly due to no-reflow phenomenon and distal embolization.[2] Large interest has been focused on the adjunctive administration of Gp IIb-IIIa inhibitors to improve perfusion and mortality. A previous meta-analysis of randomized trials[3–16] has shown significant benefits in mortality and re-infarction.[17] However, these benefits have disappeared in recent large randomized trials

* Corresponding author. Tel: +39 0321 3733141, Fax: +39 0321 3733407, Email: giuseppe.deluca@maggioreosp.novara.it

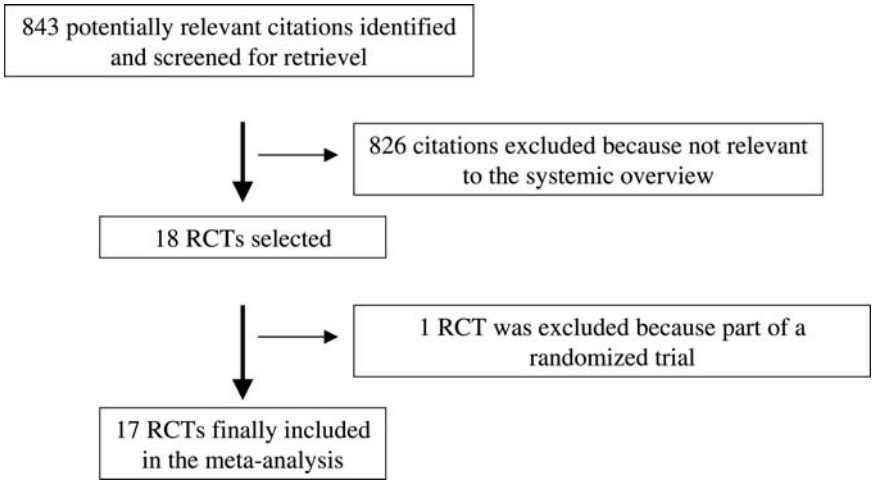

Figure 1 Flow diagram of the systematic overview process. RCT, randomized controlled trials.

(BRAVE-3 and HORIZONS trials)[18,19] conducted on the top of clopidogrel administration. However, the relatively low mortality may have hampered the conclusion of these recent trials. Thus, the aim of the current study was to perform an update meta-analysis of randomized trials on adjunctive Gp IIb-IIIa inhibitors in primary angioplasty, and to evaluate by meta-regression analysis, whether the results may be related to risk profile.

Methods

Eligibility and search strategy

We obtained results from all randomized trials evaluating the benefits of adjunctive Gp IIb-IIIa inhibitors among STEMI patients undergoing primary angioplasty. The literature was scanned by formal searches of electronic databases (MEDLINE and CENTRAL) from January 1990 to September 2008. Furthermore, oral presentations and/or expert slide presentations were included [searched on the TCT (www.tctmd.com), EuroPCR (www.europcr.com), ACC (www.acc.org), AHA (www.aha.org), and ESC (www.escardio.org) websites from January 2002 to September 2008].The following key words were used: randomized trial, myocardial infarction, reperfusion, primary angioplasty, Gp IIb-IIIa inhibitors, abciximab, tirofiban, and eptifibatide.

Inclusion criteria were: (i) randomized treatment allocation; (ii) availability of complete clinical data. Exclusion criteria: (i) follow-up data in less than 90% of patients; (ii) ongoing studies or irretrievable data. No language restrictions were enforced.

Data extraction and validity assessment

Data were independently abstracted by two investigators. In case of incomplete or unclear data, authors, where possible, were contacted. Disagreements were resolved by consensus. Data were managed according to the intention-to-treat principle.

Outcome

Primary and secondary endpoints were mortality and re-infarction at 30 days, respectively. Safety endpoint was the rate of major bleeding complications.

Data analysis

Statistical analysis was performed using the Review Manager 4.27, SPSS 15.0 statistical package and Comprehensive Meta-analysis Version 2. Odds ratio (OR) and 95% confidence intervals (95% CI) were used as summary statistics. The pooled OR was calculated by using a fixed-effect model with the Mantel–Haenszel method. The DerSimonian and Laird random effect model was additionally applied to calculate pooled OR in case of significant heterogeneity across studies. Between-study heterogeneity was analysed by means of $I^2 = [(Q - df)/Q] \times 100\%$, where Q is the χ^2 statistic, and df is its degrees of freedom. The potential publication bias was examined by constructing a 'funnel plot', in which the standard error (SE) of the ln OR was plotted against the OR (30 day mortality).

The relationship between benefits in mortality and risk profile in each study (study level variable) was evaluated by a weighted random-effects meta-regression analysis regressing the log OR against the control group event rate expressed as odds using the inverse of the variance of the log OR as weight.[20]

We additionally performed a weighted random-effects meta-regression analysis regressing the log OR against the average log event rate observed in experimental and control group combined, using the inverse of the variance of the log OR as weight[20] and a weighted random-effects meta-regression analysis regressing the log odds in the experimental group against the log odds in the control group, using the inverse of the variance of the log odds as weight.[21]

Results are reported as beta coefficients and two-sided *P*-values. Similar analysis was conducted for 30 day re-infarction.

The study was performed in compliance with the Quality of Reporting of Meta-Analyses (QUORUM) guidelines.[22]

Results

Eligible studies

Of the 859 potentially relevant articles initially screened, a total of 17 trials were initially identified[3–16,18,19,23,24] (*Figure 1*). One trial[4] was excluded because part of the ISAR trial.[5] Thus, a total of 16 randomized trials[3,5–16,18,19,23,24] were finally included in the meta-analysis., involving 10 085 patients (5094 or 50.5% in the

Table 1 Characteristics of randomized trials included in the meta-analysis

Study	Period	*N*	Study-drug design (number of patients)	Primary endpoint	Major bleeding complications
RAPPORT	1995–1997	483	Abciximab ($n = 241$) vs. placebo ($n = 242$)	6 month combined death, reMI, and TVR	TIMI major bleeding
APE	1997–1998	59	Early ($n = 29$) vs. no ($n = 30$) abciximab	Myocardial perfusion	n.r.
ADMIRAL	1997–1998	300	Stenting + abciximab ($n = 151$) vs. placebo ($n = 149$)	30 day combined death, reMI, urgent TVR	TIMI major bleeding
CADILLAC	1997–1999	2082	Abciximab + stent ($n = 524$) or balloon ($n = 528$), control + stent ($n = 512$), or balloon ($n = 518$)	6-month combined death, reMI, TVR, or disabling stroke	Not defined
Petronio *et al.*	1998–2000	89	Abciximab ($n = 44$) vs. placebo ($n = 45$)	6 month combined death, reMI, heart failure, TLR	Substantial haemodynamic compromise requiring treatment
ISAR-2	1997–1998	401	Stenting ($n = 200$) vs. abciximab + stenting ($n = 201$)	6 month angiographic restenosis	Intracranial haemorrhage, bleeding requiring surgery or transfusion
ACE	2001–2002	400	Stenting ($n = 200$) vs. abciximab + stenting ($n = 200$)	Combined death, reMI stroke, and target vessel	Stroke, bleeding requiring transfusion or vascular repair
Zorman *et al.*	1998–2001	163	Early ($n = 56$) vs. late (postangiography; $n = 56$) abciximab vs. placebo ($n = 51$)	Early (60 min) ST-segment resolution	Not defined
Petronio *et al.*	n.r	31	Abciximab ($n = 17$) vs. control ($n = 14$)	Myocardial perfusion and functional recovery at 30 days	TIMI major bleeding
Petronio *et al.*	n.r	90	Abciximab ($n = 30$) vs. adenosine ($n = 30$) vs. control ($n = 30$)	LV remodelling	GUSTO
Steen *et al.*	2000–2002	53	Tirofiban ($n = 24$) vs. control ($n = 29$)	Myocardial perfusion	n.r.
Ernst *et al.*	2002–2003	112	Abciximab ($n = 28$) or tirofiban ($n = 29$) or high-dose tirofiban ($n = 28$) vs. control ($n = 27$)	Platelet aggregation inhibition	Blood transfusion or surgery, intracranial or peritoneal haemorrhage
Lee *et al.*	n.r.	68	Abciximab ($n = 32$) vs. control ($n = 36$)	Myocardial salvage	n.r.
BRAVE-3	2004–2007	800	Abciximab ($n = 401$) vs. placebo ($n = 399$)	Infarct size	n.r.
HORIZONS-MI	2005–2007	3602	Glycoprotein IIb-IIIa inhibitors ($n = 1800$) vs. bivalirudine ($n = 1802$)	Net clinical outcome and major bleeding complications	TIMI major bleeding
On-TIME 2	2007–2008	984	Early high-dose tirofiban ($n = 491$) vs. placebo ($n = 493$)	Residual cumulative ST-deviation	TIMI major bleeding
ASSIST	2005–2008	400	Eptifibatide ($n = 201$) vs. placebo ($n = 199$)	Death, re-infarction, recurrent severe ischaemia at 30 days	TIMI major bleeding

Abciximab dose: 0.25 mg/kg IV bolus followed by 12 h infusion at 0.125 mg kg^{-1} min^{-1}. Eptifibatide dose: 2 boluses of 180 mg/kg IV 10 min apart, then 2.0 mg kg^{-1} min^{-1} infusion. Tirofiban: 10 μg/kg bolus and 0.15 μg/kg/min infusion over 24 h. High-dose tirofiban: bolus of 25 μg/kg, followed by a 12 h infusion at 0.15 μg/kg/min.
n.r., not reported; reMI, re-infarction; TVR, target vessel revascularization; LV, left ventricle.

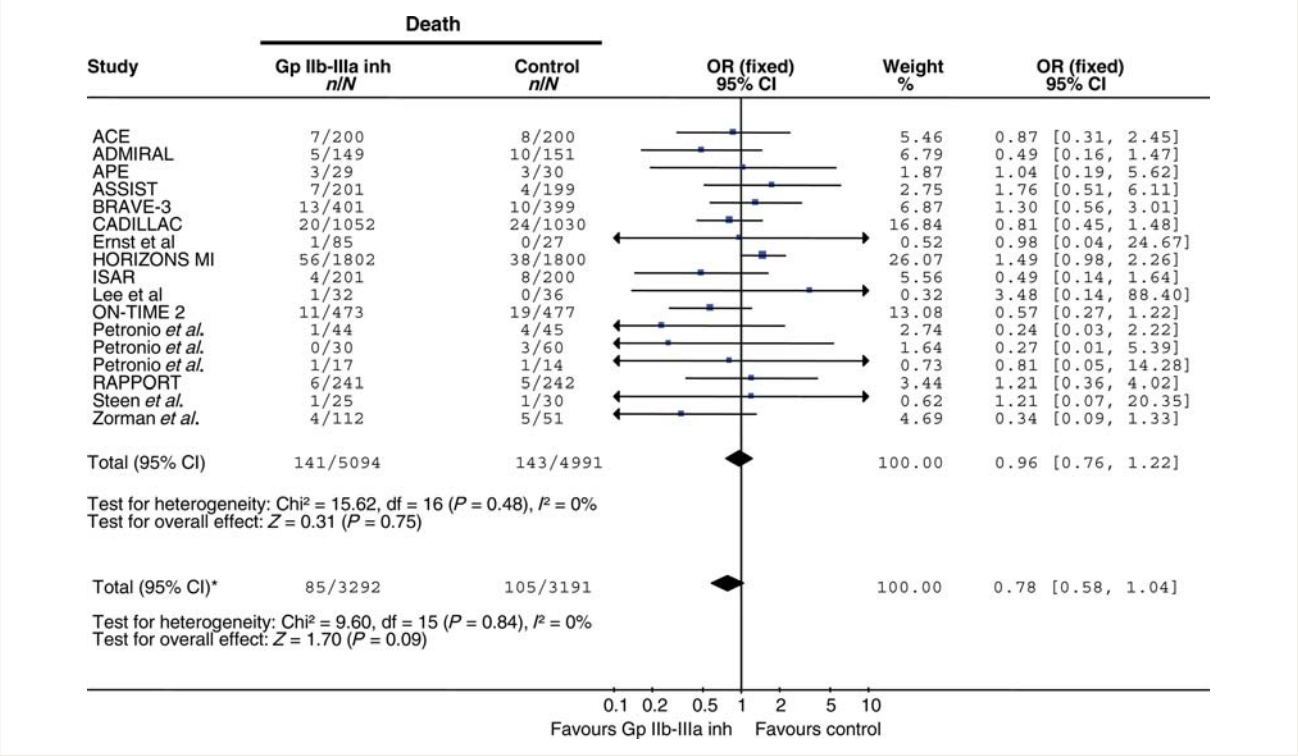

Figure 2 Glycoprotein IIb-IIIa inhibitors and mortality benefits at 30 day follow-up, with odds ratios and 95% confidence intervals (CI). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. *Without Horizon trial.

Gp IIb-IIIa inhibitors group and 4991 or 49.5% in the control group). Characteristics of the included trials are shown in *Table 1*. High-dose bolus (600 mg) of clopidogrel was administrated in only three trials,[19,23,24] whereas in the Horizons trial[18] the dosage of bolus of clopidogrel was left to the discretion of the treating physicians. In the study by Zorman *et al.*,[10] patients were randomized to early vs. late administration (in the cath lab) or no abciximab. In the Horizons trial,[18] the control group received Bivalirudin as anticoagulation therapy instead of unfractionated heparin.

Primary endpoint

As shown in *Figure 2*, overall Gp IIb-IIIa inhibitors did not reduce 30 day mortality [2.8 vs. 2.9%, OR (95% CI) = 0.96 (0.76–1.22), $P = 0.75$, $P_{het} = 0.48$, NNT = 1000]. A trend in benefits in mortality was observed after the exclusion of the Horizons trial [2.6 vs. 3.3%, OR (95% CI)= 0.78 (0.58, 1.04), $P = 0.09$, $P_{het} = 0.84$; NNT = 143]. As shown in *Figure 3*, no publication biased was observed.

As shown in *Figure 4A*, we observed a relationship between patient's risk profile and mortality benefits from adjunctive Gp IIb-IIIa inhibitors (beta = −14.12, $P = 0.008$; without Horizons: beta = −10.31, $P = 0.08$). The relationship was confirmed when benefits were plotted against average events between experimental and control groups (beta = 0.68, $P = 0.07$; without Horizons: beta = −0.47, $P = 0.23$) (*Figure 4B*). No significant relationship was observed between the odds of the experimental and control groups (beta = 0.23, $P = 0.21$; without Horizons: beta = 0.40, $P = 0.06$) (*Figure 4C*). In particular, the deviation of the regression line, corresponding to the pooled treatment effect, from the line of identity (*Figure 4C*) suggests heterogeneity and further supports the relationship between risk profile and mortality benefits.

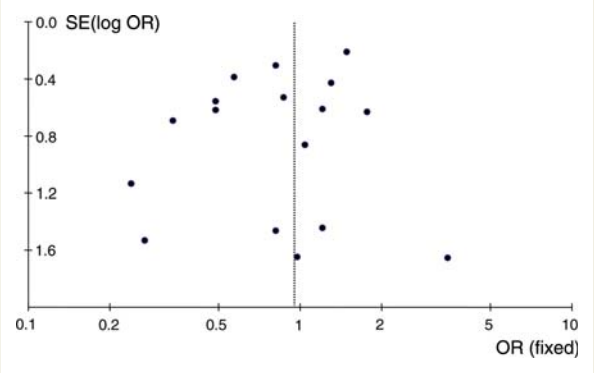

Figure 3 Funnel plot of all studies included in the meta-analysis. Sample size of each study was plotted against the odds ratio for 30 day mortality. No skewed distribution was observed, suggesting no publication bias.

Secondary endpoint

As shown in *Figure 5*, overall Gp IIb-IIIa inhibitors did not reduce 30 day re-infarction [1.5 vs. 1.9%, OR (95% CI) = 0.82 (0.59–1.13), $P = 0.22$, $P_{het} = 0.54$; NNT = 250]. Similar findings were observed after the exclusion of the Horizons trial [1.3 vs.

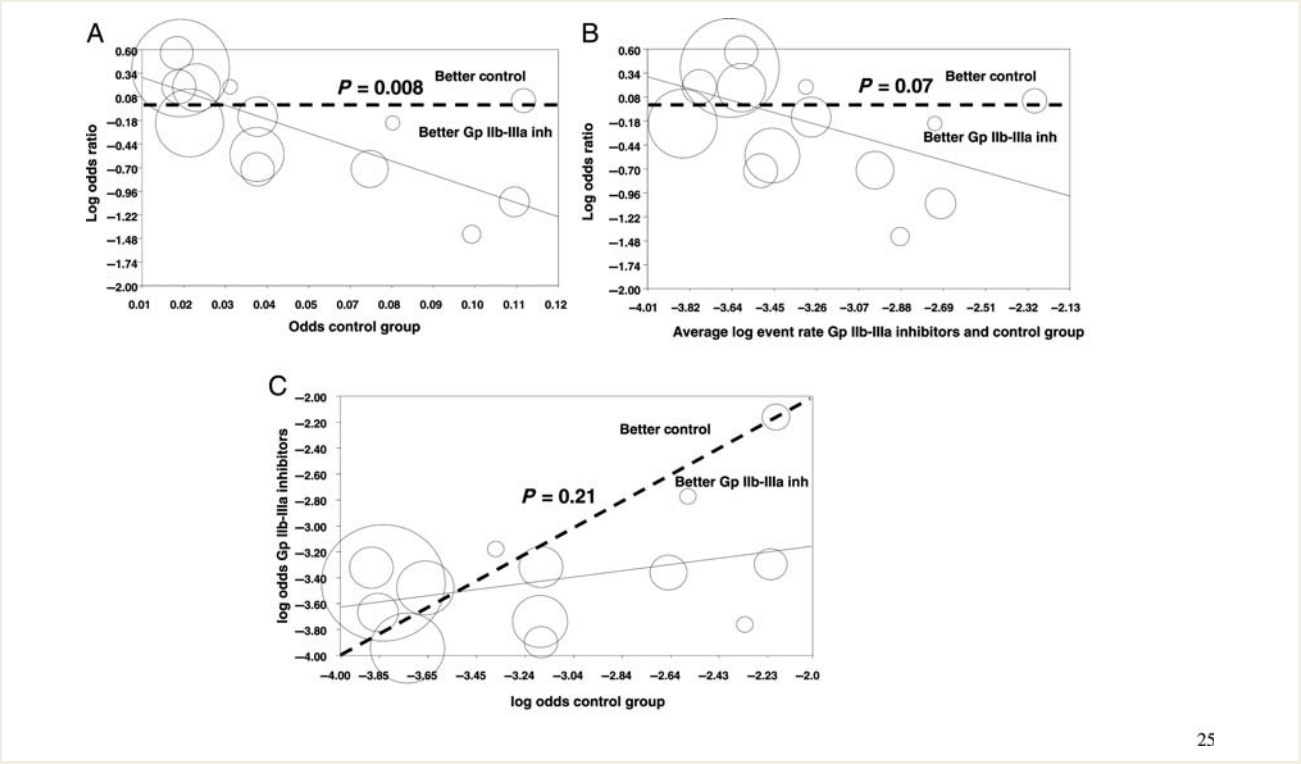

Figure 4 (*A*) Weighted random-effects meta-regression analysis regressing the log odds ratio of mortality against the control group mortality rate expressed as odds using the inverse of the variance of the log odds ratio as weight; this graph shows a relationship between risk profile and mortality benefits from Gp IIb-IIIa inhibitors. (*B*) Weighted random-effects meta-regression analysis regressing the log odds ratio of mortality against the average log mortality rate observed in experimental and control group combined, using the inverse of the variance of the log odds ratio as weight; this graph shows a relationship between risk profile and mortality benefits from Gp IIb-IIIa inhibitors. (*C*) Weighted random-effects meta-regression analysis regressing the log odds of mortality in the experimental group against the log odds of mortality in the control group, using the inverse of the variance of the log odds as weight; this graph suggests heterogeneity and confirm previous findings. In fact, the line corresponding to the pooled treatment effect is not parallel to the line of identity (dashed line), as expected in case of homogeneous trials, but deviates from it.

1.9%, OR (95% CI) = 0.70 (0.46–1.08), $P = 0.11$, $P_{het} = 0.5$; NNT = 167].

As shown in *Figure 6A*, no significant relationship was observed between the risk of re-infarction and benefits from adjunctive Gp IIb-IIIa inhibitors (beta = −17.88, $P = 0.25$; without Horizons: beta = −10.31, $P = 0.08$). These data were confirmed when the benefits were plotted against average events between experimental and control groups (beta = −0.10, $P = 0.79$; without Horizons: beta = −0.47, $P = 0.23$) (*Figure 6B*). A significant relationship was observed between the odds of the experimental and control groups (beta = 0.55, $P = 0.03$; without Horizons: beta = 0.48, $P = 0.12$) (*Figure 6C*), with a minor deviation of the regression line from the line of identity when compared with that observed for mortality.

Safety endpoint

As shown in *Figure 7*, Gp IIb-IIIa inhibitors were associated with higher risk of major bleeding complications [3.9 vs. 2.6%, OR (95% CI) = 1.50 (1.19–1.89), $P = 0.0005$, $P_{het} = 0.85$]. Similar results were observed after exclusion of the Horizons trial [3.3 vs. 2.3%, OR (95% CI) = 1.41 (1.04, 1.93), $P = 0.03$, $p_{het} = 0.8$].

Discussion

The main finding of this meta-analysis is that among STEMI patients undergoing primary angioplasty, there is a significant relationship between risk profile and benefits from adjunctive Gp IIb-IIIa inhibitors in terms of mortality at 30 day follow-up.

Several randomized trials have shown that primary angioplasty is superior to thrombolysis. However, despite primary angioplasty is able to restore TIMI 3 flow in the vast majority of patients, a relatively large proportion of patients experience poor reperfusion.[2] In the last years, growing interests have been focused on the role of distal embolization as major determinant of poor reperfusion.[2] Gp IIb-IIIa inhibitors are the most powerful class of antiplatelet therapies, and their adjunctive beneficial effects have been shown in several randomized trials.

In the ACE trial,[13] a total of 400 STEMI patients were randomized to abciximab or placebo, all patients treated with stent implantation. In this study, conducted without strict exclusion criteria, and thus with mortality rates close to daily clinical practice, abciximab was associated with a significantly improved survival and re-infarction. The benefits in mortality have been confirmed at long-term follow-up.[25]

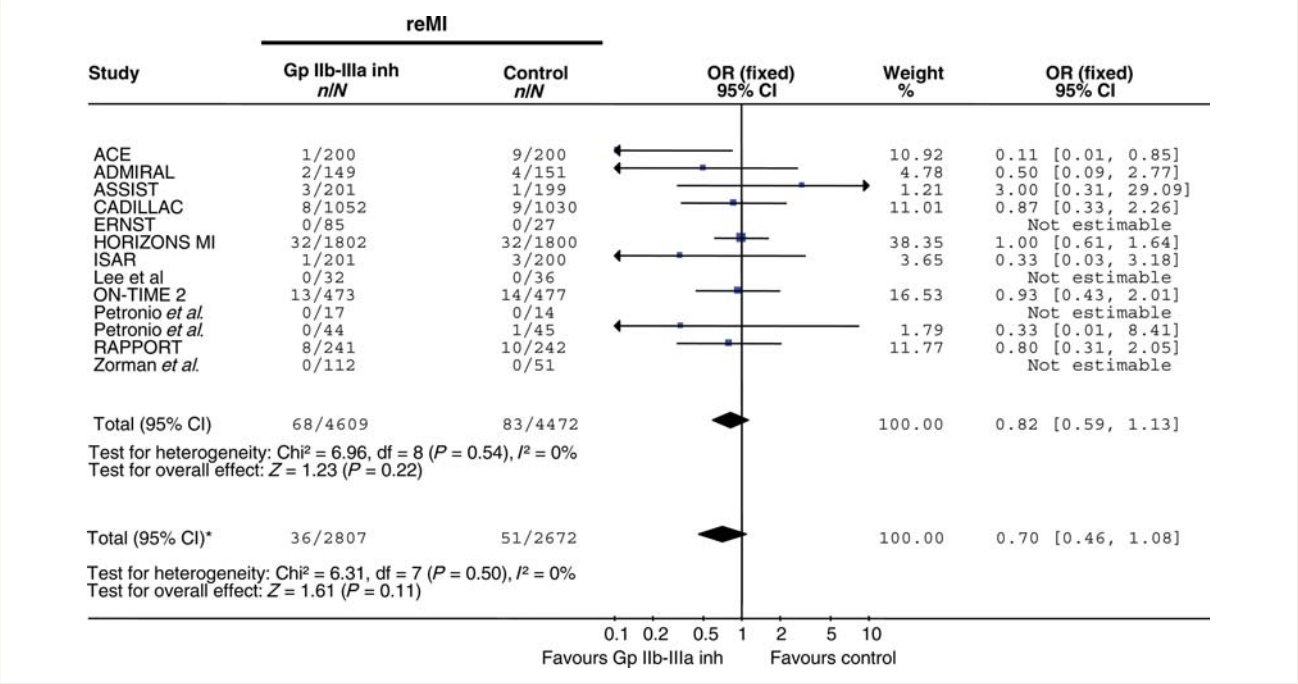

Figure 5 Glycoprotein IIb-IIIa inhibitors and benefits in re-infarction at 30 day follow-up, with odds ratios and 95% confidence intervals (CI). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. *Without Horizon trial.

Several recent large randomized trials have been conducted to explore the benefits from adjunctive Gp IIb-IIIa inhibitors on the top of clopidogrel administration, with contrasting results.[18,19,23,24]

In the BRAVE-3 trial,[19] a total of 800 patients were randomized to abciximab or placebo before angioplasty, on the top of 600 mg. This study did not show benefits either in the primary endpoint (infarct size as estimated by scintigraphic techniques) or mortality (2.5 vs. 3.2%). It must be remarked that even though the aim of the study was to evaluate the impact of abciximab on infarct size, the median ischaemia time was 4.5 h. It may be arguable whether any adjunctive therapy in the late phase of 'golden hours' would provide adjunctive benefits in terms of infarct size. Furthermore, the risk profile was relatively low to evaluate the benefits in terms of clinical outcome.

In the large HORIZONS trial,[18] 3602 STEMI patients were randomized to heparin + Gp IIb-IIIa inhibitors were compared with bivalirudin. Patients received 300 or 600 mg clopidogrel loading dose (the decision was left to the physician's discretion). Bivalirudin was surprisingly associated with a mortality reduction, despite the significantly higher rate of acute in-stent thrombosis. As for the BRAVE-3 trial,[19] a relatively low-risk population has been enrolled in this trial, that would have privileged bleeding complications over thrombotic complications. In the recent On-TIME-2 trial,[21] a total of 985 patients were randomized on the top of 600 mg clopidogrel loading dose to early high-dose tirofiban vs. placebo (it was allowed periprocedural bail-out administration). Early tirofiban administration was associated with benefits in mortality (2.3 vs. 4%), even though the difference was not statistically significant due to the fact that the trials was underpowered to detect a significant reduction in mortality. However, by pooling data of 414 open-label patients (patients randomized in two Dutch centres as pilot phase) and 984 patients included in the double-blind study (with a total of 1398 patients) tirofiban administration was associated with reduced mortality (2.2 vs. 4.1%, $P = 0.051$).

In the current meta-analysis, we observed a significant relationship between risk profile and benefits in mortality, but not re-infarction, from adjunctive Gp IIb-IIIa inhibitors. Thus, since clopidogrel administration takes 3–4 h to reach the top of inhibition of platelet aggregation,[26] Gp IIb-IIIa inhibitors should be considered to rapidly inhibit platelets, with subsequent benefits in mortality according to the risk profile. The use of risk scores, such as the TIMI Risk Score,[27] should be strongly encouraged to identify a higher risk population with thrombotic complications largely outweighing the risk of bleeding complications, and thus who may subsequently benefit in terms of mortality from aggressive antithrombotic therapy.

Despite the negative results of the FINESSE trial,[28] early administration may certainly be encouraged due to the benefits with early administration observed in the Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up (ADMIRAL) trial,[7] and in several recent reports,[29–31] including On-TIME 2 trial.[23]

Limitations

The use of a risk score based on individual patient's data would have overcome the limitation due to the use of mortality in control group as marker of risk profile.[19] In fact, the observed proportions of events in the control groups of the trials, as a measure of the underlying risk, may produce misleading results. This arises

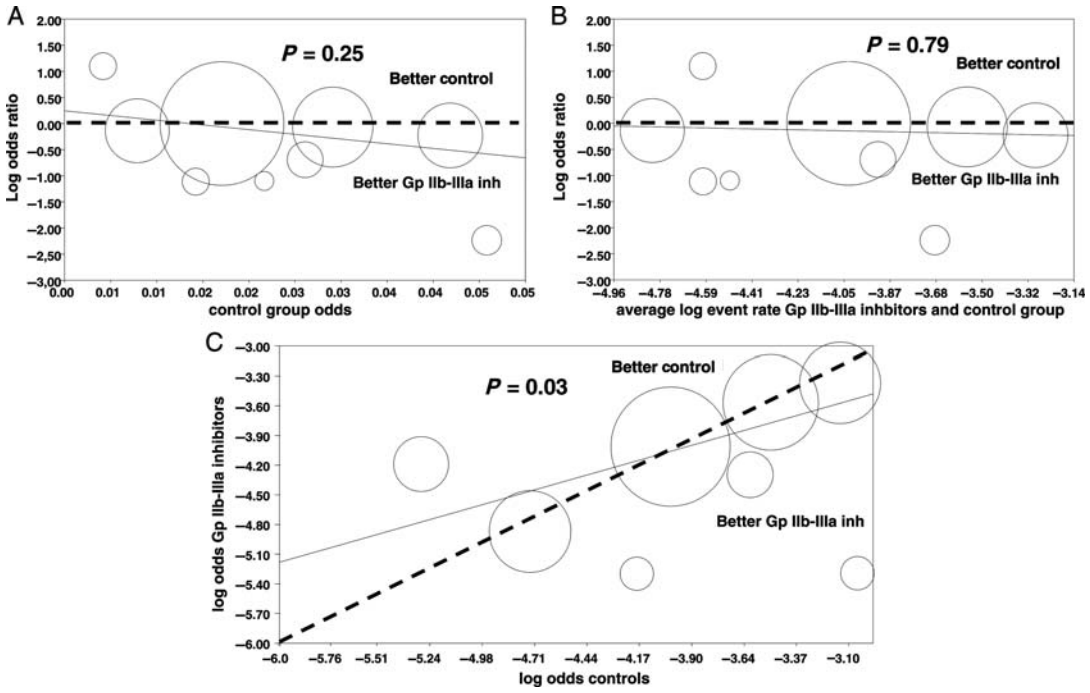

Figure 6 (*A*) Weighted random-effects meta-regression analysis regressing the log odds ratio of re-infarction against the control group re-infarction rate expressed as odds using the inverse of the variance of the log odds ratio as weight; this graph shows no relationship between risk profile and benefits in re-infarction from Gp IIb-IIIa inhibitors. (*B*) Weighted random-effects meta-regression analysis regressing the log odds ratio of re-infarction against the average log re-infarction rate observed in experimental and control group combined, using the inverse of the variance of the log odds ratio as weight; this graph shows no relationship between risk profile and benefits in re-infarction from Gp IIb-IIIa inhibitors. (*C*) Weighted random-effects meta-regression analysis regressing the log odds of re-infarction in the experimental group against the log odds of re-infarction in the control group, using the inverse of the variance of the log odds; the line corresponding to the pooled treatment effect deviates of a minor extent from the line of identity (dashed line), when compared with that observed for mortality, confirming previous findings.

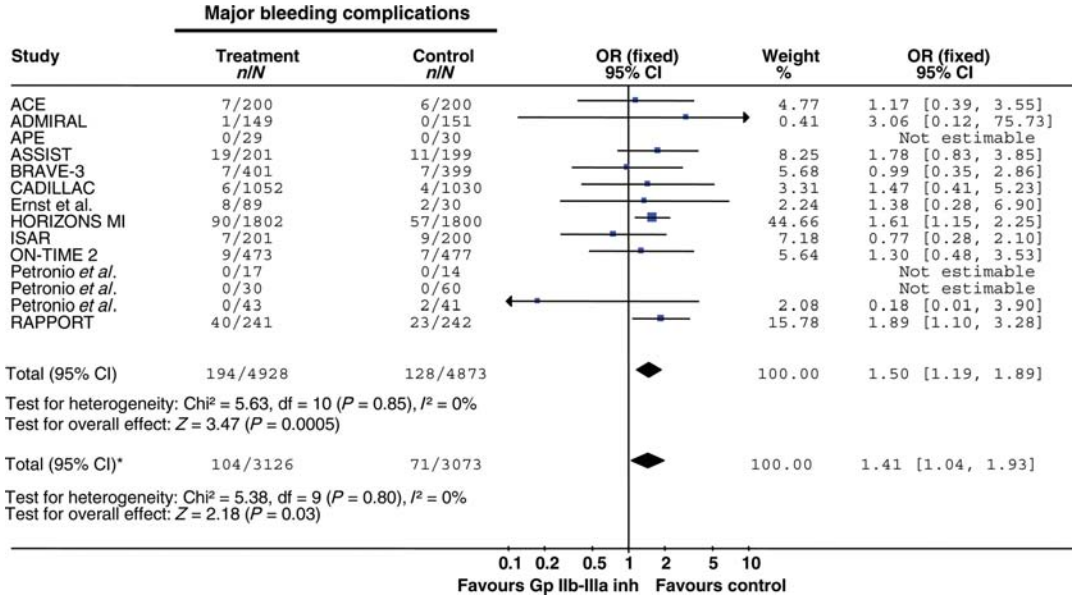

Figure 7 Glycoprotein IIb-IIIa inhibitors and major bleeding complications at 30 day follow-up, with odds ratios and 95% confidence intervals (CI). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. *Without Horizon trial.

through a bias due to regression to the mean, especially observed in meta-analyses which include some small trials or in which the variability in the true underlying risks across trials is small. In order to minimize this limitation and to confirm initial findings, we have performed additional analyses thought to be more appropriate such as the use of average proportion of events in the control and treated groups as the measure of underlying risk or to plot the proportion of events in the treated group against that in the control group.[20]

Even though high-dose clopidogrel bolus may obtain a quicker and better platelet aggregation inhibition, the peak effect is still observed after 3–4 h,[26] whereas Gp IIb-III inhibitors act very rapidly. In fact, benefits from Gp IIb-IIIa inhibitors were observed in the On-TIME 2 trial[23] despite early administration of high-dose 600 mg clopidogrel, whereas in the BRAVE trial[19] clopidogrel was administrated just before the procedure and thus less probably affecting the results of the study. However, due to paucity of data, no definite conclusion can be drawn on this issue. In addition, we analysed short-term outcomes, whereas some Gp IIb-IIIa inhibitor studies have demonstrated increased survival benefit with longer follow-up.[25] No uniform definition of major bleeding complications was adopted in trials included in the current meta-analysis. Finally, we could not exclude a clinical heterogeneity between studies, due to different inclusion and exclusion criteria, and study drugs.

Conclusions

This meta-analysis shows a significant relationship between benefits in mortality from Gp IIb-IIIa inhibitors and patient's risk profile. Thus, Gp IIb-IIIa inhibitors should be strongly considered among high-risk patients.

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CARDIOVASCULAR FLASHLIGHT

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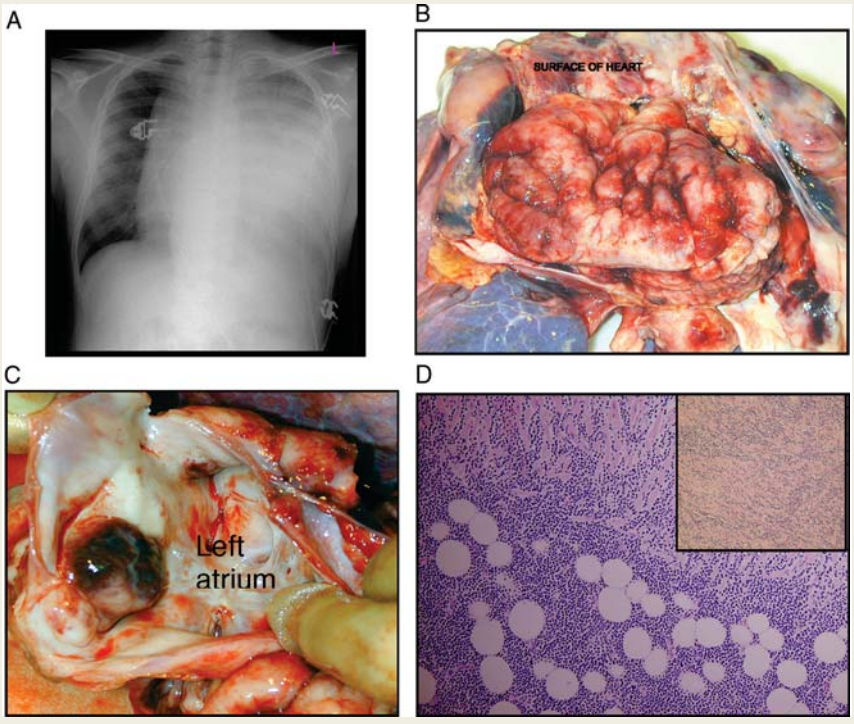
Primary cardiac T-cell lymphoma in a child

Junaid Patel[1,2]* and Mary N. Sheppard[1,2]

[1]CRY Centre for Cardiac Pathology, National Heart and Lung Institute, Imperial College, London, UK and [2]Department of Histopathology, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK

* Corresponding author. Tel: +44 20 7351 8424, Fax: +44 20 7351 8293, Email: junaid.patel@ic.ac.uk

A 10-year-old boy presented with a 12-week history of progressive breathlessness following a chest infection. He had no history of pyrexia or night sweats and no significant weight loss. On examination, the patient was well at rest but breathless on minimal exertion. He was slightly pale with palpable cervical lymph nodes. His heart rate was 136 b.p.m. and blood pressure 107/75. On auscultation, heart sounds were muffled with no audible murmurs, and his chest was clear. Blood tests were normal but a chest X-ray showed a massive cardiomegaly (*Panel A*). An echocardiogram showed a large pericardial effusion which was compromising the function of the heart. A pericardial drain was inserted and the patient was unstable throughout the procedure with bradycardia requiring adrenaline boluses. Later the same day, he had a cardiac arrest and cardiopulmonary resuscitation (CPR) was commenced. A sternotomy was performed to see if there was any reversible cause of cardiac arrest. The findings were of an infiltrating cardiac tumour surrounding the left and right ventricle. There was no residual effusion. In view of these findings and the prolonged resuscitation, CPR was discontinued and the patient confirmed dead.



At post-mortem there was a widespread malignant tumour involving the external surface of both ventricles (*Panel B*) with extension into the roof of the left atrium (*Panel C*) and adjacent visceral and parietal pericardium. He also had widespread involvement of all mediastinal lymph nodes. Histology confirmed the diagnosis of a primary cardiac T-cell lymphoblastic lymphoma (*Panel D*).

Panel A. A chest X-ray (CXR) showing a massive cardiomegaly.

Panel B. Widespread malignant tumour involving the external surface of both ventricles.

Panel C. Widespread malignant tumour involving the external surface of both ventricles with extension into the roof of the left atrium.

Panel D. Histology showing infiltration of right and left ventricles by small malignant lymphoid cells. (Haematoxylin and eosin stain, magnification ×400). Inset: The cells stained positively for CD3.